

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.

Paper No. 51

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE BOARD OF PATENT APPEALS  
AND INTERFERENCES

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Ex parte JERALD C. SADOFF, STEVEN M. OPAL,  
ALAN S. CROSS, and MARK W. BODMER

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Appeal No. 1997-4275  
Application No. 08/253,217

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ON BRIEF

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Before WINTERS, ROBINSON, and MILLS, Administrative Patent Judges.  
ROBINSON, Administrative Patent Judge.

**DECISION ON APPEAL**

This is a decision on the appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 1 - 9 and 13 - 16, which are all of the claims pending in the application.

Claims 1 and 13 are illustrative of the subject matter on appeal and read as follows:

1. A pharmaceutical composition comprising an antibody to tumor necrosis factor (anti-TNF) and an antibody to bacterial lipopolysaccharide (anti-LPS) as a combined preparation for simultaneous mixed, simultaneous separate or sequential use in the therapy of sepsis.
13. A method for the treatment of sepsis in a human or animal subject, the method comprising administering to said subject an effective amount of the combination of an anti-TNF antibody in conjunction with an anti-LPS antibody.

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The references relied upon by the examiner are:

Ziegler et al. (Ziegler), "Treatment of Gram-Negative Bacteremia and Shock with Human Antiserum to a Mutant Escherichia Coli," The New England Journal of Medicine, Vol. 307, No. 20, pp. 1225-1230 (1982)

Beutler et al. (Beutler), "Passive Immunization Against Cachectin/Tumor Necrosis Factor Protects Mice from Lethal Effect of Endotoxin," Science, Vol. 229, pp. 869-871 (1985)

### **Ground of Rejection**

Claims 1 - 9 and 13 - 16 stand rejected under 35 U.S.C. § 103(a). As evidence of obviousness, the examiner relies on Ziegler and Beutler.

We reverse.

### **Discussion**

In reaching our decision in this appeal, we have given careful consideration to the appellants' specification and claims and to the respective positions articulated by the appellants and the examiner. We make reference to the Examiner's Answer of March 14, 1997 (Paper No. 46) for the examiner's reasoning in support of the rejection and to the appellants' Brief on Appeal, filed December 11, 1996<sup>1</sup> (Paper No. 44), and Reply Brief, filed May 14, 1997 (Paper No. 47) for the appellants' arguments thereagainst.

### **Background**

Applicants describe the claimed invention at page 1 of the Specification as providing a composition comprising an antibody to tumor necrosis factor alpha (TNF-")

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<sup>1</sup> We note that the "Contents" portion of the file wrapper for this application incorrectly indicates that the Appeal Brief was filed December 11, 1997.

and an antibody to lipopolysaccharide (LPS) which is useful for treating and preventing sepsis in patients with bacterial infections.

**The rejection under 35 U.S.C. § 103(a)**

The appealed claims stand rejected under 35 U.S.C. § 103(a) as being obvious over the combined teachings of Ziegler and Beutler.

The examiner relies on Ziegler as describing the use of anti-LPS antibody for the treatment of gram negative bacteremia and shock, which is sepsis. (Answer, page 3).

Appellants do not dispute the examiner's interpretation of the Ziegler reference.

The examiner relies on Beutler as teaching (Answer, page 5):

that anti-TNF antibody protects mice from the lethal effects of endotoxin LPS produced by E.coli. Beutler et al. teach that TNF is produced in vivo and in vitro in response to LPS challenge (page 869, col. 3). Therefore, they passively immunized mice with anti-TNF antibody and challenged the mice with lethal doses of LPS. They were able to demonstrate that the LD<sub>50</sub> of LPS in mice treated with the immune serum was significantly higher than the LD<sub>50</sub> for the control mice (Fig. 3) and this shift was dose dependent (Table 1). Beutler et al. concluded that a role of TNF was to mediate the lethal effects of LPS because mice that were injected with anti-TNF antibody prior to the administration of LPS fared better than those passively immunized at the moment LPS injection or thereafter (page 871, col. 1).

The examiner does not argue that either reference explicitly describes or suggests a combination of an antibody to TNF and an antibody to bacterial LPS or the use of such a combination to treat sepsis in a human, as presently claimed.

The examiner urges that the use of two materials in combination would have been prima facie obvious where each is known to function for the same purpose. (Answer, page 17). The examiner urges that (id.):

each antibody is independently useful for the treatment of bacterial/LPS infection because Ziegler et al. outright show this treatment with anti-LPS antibody and Beutler et al. state that such treatment with anti-TNF antibody is an “obvious corollary” to their study.

Thus, the examiner concludes (Answer, page 20):

We have two different active sites within the same pathway, and two different drugs/antibodies which act independently on each of the active sites of the pathway. Absent contradictory evidence, it is concluded that the administration of these two antibodies would be expected to have additive or synergistic effects when combined for the treatment of sepsis.

As the examiner realizes, the disclosure of Beutler is critical to the question of whether a prima facie case of obviousness of the claimed subject matter is established on this record. The examiner has provided an in depth analysis of Beutler supported by sound scientific reasoning. (Answer, pages 7-14). However, in our opinion, the examiner has extended the teaching of Beutler in concluding that this reference suggests the use of an antibody to TNF for the treatment of sepsis in patients. Beutler describes tests wherein mice are given a toxic dose of LPS in a single administration

wherein the mice are treated with the antibody to TNF at 6 and 3 hours prior to administration of LPS, at the time of administration of LPS and 3 and 6 hours after the administration of LPS. The results are summarized in Fig. 4. In describing the observed results Beutler states (page 871, column 1):

The time at which the antiserum was administered relative to the time of LPS administration was found to be of crucial importance in producing a protective effect. Mice that were injected with immune serum 3 or 6 hours prior to administration of LPS fared better than those passively immunized at the time of LPS injection or several hours after (Fig. 4). (Emphasis added).

The examiner interprets the stated conclusion reached by Beutler that “The potential utility of passive immunization with antisera to cachectin/TNF in animals with shock induced by septicemia. . . needs further exploration” as establishing that the “obvious corollary is the possibility that agents which affect the synthesis or binding of cachectin/TNF to its receptor might be of utility in this setting without compromising the host’s immune system.” (Answer, page 12).

We would agree with the examiner’s findings that Beutler describes results which reasonably suggest that passive immunization with antisera to cachectin/TNF protects against the effect of LPS which may result in death. However, we do not agree that this teaching describes or suggests a treatment in human patients which are exhibiting the clinical symptoms of sepsis. The data representative of the

administration of the TNF antibody after the administration of LPS provides, at best, questionable benefit to the treated mice. Beutler would reasonably appear to recognize this in the stated conclusion which emphasized the criticality of timing of the administration of the antibody. Further, we do not agree that Beutler would reasonably suggest a treatment of patients with a bacterial infection which could result in sepsis using the antibody to TNF to prevent or ameliorate the effect of LPS. As acknowledged by the examiner "the experiments performed in Beutler et al. were done to determine if TNF mediated the lethal effects of LPS, not to treat the sepsis and prevent death in the mice in which they administered the LPS." (Answer, page 9).

Beutler states (page 871, col. 1):

These data give evidence for the role of cachectin/TNF in mediating the lethal effects of LPS. Cachectin/TNF is clearly only one of the mediators responsible for the numerous pathological effects evoked by LPS, since the passively immunized mice become febrile, and continue to appear ill and distressed. It is possible, for example, that cachectin/TNF acts in concert with other mediators . . . in order to elicit the lethal effect of LPS.

While Beutler may speculate about the "potential utility" of passive immunization with antisera to cachectin/TNF in animals with shock. . . ." (page 871, column 1, last paragraph), Beutler stops short of describing such a treatment or of suggesting that such a treatment would likely be beneficial in the treatment or prevention of sepsis.

Thus, we conclude that Beutler does not evince the use of antibodies to TNF for the treatment or prevention of sepsis in a patient with a bacterial infection. The examiner's

conclusion of obviousness of the claims directed to both the composition and method of use is based, at least in part, on the proposition that Beutler establishes the use of antibodies for TNF to prevent or treat patients with sepsis. Thus, this conclusion is not adequately supported by the facts or evidence present in this record. In our opinion, the combined teachings of Beutler with Ziegler are not sufficient to support a conclusion that the presently claimed invention would have been prima facie obvious to one of ordinary skill in this art at the time of the invention.

In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a prima facie case of obviousness. In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Only if that burden is met, does the burden of coming forward with evidence or argument shift to the applicants. Id. Where the examiner fails to establish a prima facie case, the rejection is improper and will be overturned. In re Fine, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir.1988). Therefore, the rejection of claims 1 - 9 and 13 - 16 under 35 U.S.C. § 103 is reversed.

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**Summary**

The rejection of claims 1 - 9 and 13 - 16 under 35 U.S.C. § 103 as unpatentable over the combined teachings of Ziegler and Beutler is reversed.

**REVERSED**

SHERMAN D. WINTERS	)	
Administrative Patent Judge	)	
	)	
	)	
	)	BOARD OF PATENT
DOUGLAS W. ROBINSON)	)	
Administrative Patent Judge	)	APPEALS AND
	)	
	)	INTERFERENCES
	)	
DEMETRA J. MILLS	)	
Administrative Patent Judge	)	

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SPENCER FRANK & SCHNEIDER  
SUITE 300 EAST  
1100 NEW YORK AVENUE NW  
WASHINGTON DC 20005-3955

DWR/jlb